Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Nonprescription Drug Products (DNDP)
CDER Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Drug name	Acetaminophen
TSI #	1355
TSI open (create) date	May 15, 2014
Safety Issue Name	Effects during pregnancy
Author name	Valerie Pratt, M.D.
Date	March 2, 2016

BACKGROUND

In February 2014, an article by Liew in JAMA Pediatrics reported an increased association between APAP use in pregnancy and attention deficit/hyperactivity disorder (ADHD) in the offspring.[1] Hence, TSI 1355 for acetaminophen (APAP) and effects during pregnancy was opened May 15, 2014. The Division of Epidemiology 1 (DEPI) conducted a review of this publication (RCM # 2014-689) and concluded, "The study's findings are difficult to interpret due to methodologic limitations and in the context of other existing data." DEPI recommended no regulatory action be taken at that time and continued vigilance.

In September 2014, an article by Thompson in PLOS One reported an association between acetaminophen use during pregnancy and ADHD symptoms.[2] Therefore, on January 9, 2015, the Agency issued Drug Safety Communication (DSC), *Prescription and Over-the-Counter (OTC) Pain Medicines: Drug Safety Communication – FDA Review of Possible Risks of Pain Medicine Use during Pregnancy*. The DSC stated that data are "too limited to make any recommendations" at this time, and it encouraged healthcare professionals talk with each patient about the benefits and risk of analgesic use during pregnancy, which may differ among patients and by treatment indication.

On March 18, 2015, DEPI completed a second review (RCM # 2015-387) of the literature. It concluded that "whether the association in causal in nature is still uncertain" and "preclinical data may be more informative in that regard."

The Division of Nonprescription Drug Products (DNDP) then consulted Pharmacology/Toxicology for a review of the available nonclinical data. The February 8, 2016 review concluded, "The available nonclinical data…do not describe studies in

[1] Liew Z et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014;168(4):313-320.
[2] Thompson J et al. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLOS One 2014;9(9):e108210.

animals that were adequately designed and conducted to address the question posed by OSE…at this time, the behavioral responses in animals that are most likely predictive of an ADHD response in humans are uncertain and, therefore, additional animal studies are not likely to be informative".

On March 1, 2016, DNDP, DEPI, and Nonclinical met to discuss the available data and completed reviews. It was agreed that the data do not support a causal association between acetaminophen and ADHD at this time. The January 9, 2015 DSC adequately informed the public if this issue. It was therefore agreed that TSI 1355 should be closed at this time and normal pharmacovigilance resumed.

CONCLUSION

TSI 1355 for acetaminophen (APAP) and effects during pregnancy (ADHD) was opened May 15, 2014. Since then, two DEPI reviews and a nonclinical review have been completed. Although data do not support a causal association, a DSC was released on January 9, 2015 to inform the public of this issue. As discussed at the March 1, 2016 DNDP, DEPI, and Nonclinical meeting, I recommend closing the TSI and resuming normal surveillance at this time.

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/s/

VALERIE S PRATT
03/09/2016